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Application Number NDA 21-312

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

NDA Number:	21-312
Applicant:	Schering Corporation
Name of Drug:	Clarinex™ Reditabs
Document Reviewed:	Stability data reports – Dated July 19, 2001
Statistical Reviewer:	Feng Zhou, HFD-715
Chemistry Reviewer:	Craig M. Bertha, Ph.D., HFD-820

I. Introduction

The sponsor submitted the stability data of four batches of Clarinex™ Reditabs 5 mg (NDA 21-312), packaged in aluminum foil blisters, to support its proposed 24-month shelf lives under 25°C 60%RH storage condition.

II. Sponsor's Stability Analysis

The sponsor submitted the stability data reports and the electronic stability data (in SAS transport files) on July 19, 2001. The SAS transport files contain the stability data up to 18 months for two test parameters (Assay and Moisture). The sponsor resubmitted the electronic stability data (in SAS transport file) on December 21, 2001 in response to the FDA October 19, 2001 AE letter. The SAS transport file contains the stability data up to 24 months for four parameters (Assay, Moisture, Dissolution, and Tensile strength).

The stability data of four batches were described in Table 1.

Table 1. Summary of all Stability Data Points Submitted by the Sponsor for Clarinex™ Reditabs 5mg with Blister Packaging Stored Under 25°C/60%RH Condition

		Time Point (month)						
Test Parameter	***Batch***	***0***	***3***	***6***	***9***	***12***	***18***	***24***
Assay of Desloratadine	22489F532S, 22489F533S, 22489F548S	S	S	S	S	S	S	S
	22480D773S	S	S	S	S			
Moisture	22489F532S, 22489F533S, 22489F548S	S	S	S	S	S	S	S
	22480D773S	S	S	S	S			
Dissolution	22489F532S, 22489F533S, 22489F548S	S	S	S	S	S	S	S
	22480D773S	S	S	S	S			
Tensile Strength Average and Individual	22489F532S, 22489F533S, 22489F548S	S	S	S	S	S	S	S
	22480D773S	S	S	S	S			

S = Submitted in electronic copy (December 21, 2001)

Table 2 contains the specification limits for the parameters the sponsor used to establish the stability for Clarinex™ Reditabs. The sponsor submitted the details of its estimation analysis for two parameters (Assay and Moisture) and proposed an expiration dating period of 24 months for the aluminum foil blisters packaging configuration when the drug products are stored under 25°C/60%RH condition. (p101, vol. 1)

Table 2. List of Specification limits the Sponsor Used to Establish the Stability For Clarinex™ Reditabs

Test Parameter	*Acceptance Criteria*
Assay of Desloratadine	
Moisture	Not more than
Dissolution	Q= in 4 Minutes
Tensile Strength	Average of 5 tablets:
	Individual tablet:

The sponsor claimed that the statistical methods used were in accordance with FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs Biologics." The sponsor also claimed that it used the Agency's SAS Stability Analysis Program (STAB) to perform the statistical analysis. The following statement is quoted from the resubmission on December 21, 2001 in response to the FDA October 19, 2001 AE letter:

> "Assay, moisture, dissolution at the 4-minute time point and tensile strength data are provided for the stability studies conducted at 25°C/60%RH up to 24 months for 3 batches and up to 9 months for a fourth batch. Statistical analyses of these data (not provided) continue to support our requested 24-month expiration-dating period."

Table 3 summarizes the results of sponsor's statistical analysis. (p101, vol. 1)

Table 3. Summary of Sponsor's Statistical Analyses for the Stability Batches of Clarinex™ Reditabs Stored Under 25°C/60%RH Condition

Test Parameter	*Batch*	*Model*	*Estimated Expiration Period*
Assay for Desloratadine	22480D773S	3	
	22489F532S		
	22489F533S		
	22489F548S		
Moisture	22480D773S	2	
	22489F532S		
	22489F533S		
	22489F548S		

KEY: Model 1 – common slope and common intercepts
Model 2 – common slope and separate intercepts
Model 3 – separate slopes and separate intercepts

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III. Reviewer's Stability Analysis

This reviewer independently analyzed the data in accordance with FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs Biologics."

Dr. Craig M. Bertha (chemist reviewer) requested the stability analysis of four parameters (Assay, Moisture content, Tensile strength, and Dissolution at the 4 minute sampling interval) using data from four batches (22489F532S, 22489F533S, 22489F548S, and 22480D773S). Using the stability data submitted on December 21, 2001, the results of this reviewer's analysis, presented in Table 5, are based on the evaluation of the four parameters (Assay, Moisture, Dissolution, and Tensile Strength).

In Table 5, the shortest estimated expiration-dating period — months, is based on the Tensile Strength (Average) data of four batches. However, one individual value of Tensile Strength that is lower than ——— (See Table 4). Figure 1 displays the Individual value of Tensile Strength data from batch 22489F533S and the fitted line.

Table 4. Description of Individual Tensile Strength Data

Test Parameter	*Specification*	*Mean*	*STD*	*Range*	*Batch*	*Time Point of Minimum Value*
Tensile Strength	No individual	0.31	0.05	———	22489F532S	18
Individual	———	0.32	0.06	———	22489F533S	18
		0.36	0.06	———	22489F548S	0
		0.34	0.03	———	22480D773S	9

V. Conclusion

The results of this reviewer's analysis are based on the evaluation of the four parameters (Assay, Moisture, Dissolution, and Tensile Strength) using data from four batches (three batches with data up to 24 months and one batch with data up to 9 months) for the aluminum foil blisters packaging configuration. Results of the reviewer's analysis show that the stability data support the 24-month expiration date proposed by the sponsor when the drug products are stored under 25°C/60%RH condition.

However, there is one individual data point of Tensile Strength that is lower than ——— Dr. Craig M. Bertha (chemist reviewer) will comment on this issue.

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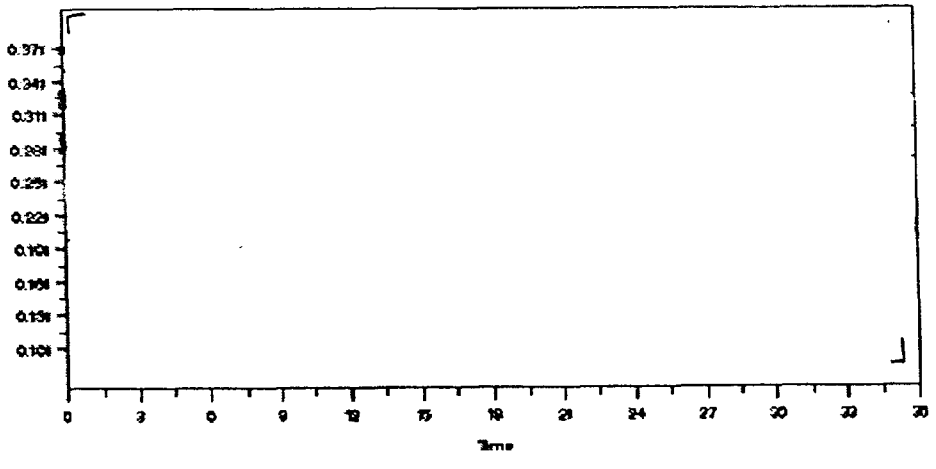
Table 5. Summary of Statistical Analyses for the Stability Batches of Clarinex™ Reditabs Stored Under 25°C/60%RH Condition

Test Parameter	*Specification*	*Strength*	*Model*	*Fitted Line*	*Batch*	*Estimated Expiration Date*
Assay for Desloratadine	of Label Claim	5 mg	2	Y = 99.7010 - 0.0209 x T	22489F532S	
				Y = 99.1295 - 0.0209 x T	22489F533S	
				Y = 99.4152 - 0.0209 x T	22489F548S	
				Y = 98.7442 - 0.0209 x T	22480D773S	
Moisture	Not more than	5 mg	2	Y = 7.1667 + 0.0066 x T	22489F532S	
				Y = 7.1239 + 0.0066 x T	22489F533S	
				Y = 7.1739 + 0.0066 x T	22489F548S	
				Y = 6.6854 + 0.0066 x T	22480D773S	
Dissolution	Not less than Q= in 4 minutes	5 mg	2	Y = 99.7010 - 0.0209 x T	22489F532S	
				Y = 99.1295 - 0.0209 x T	22489F533S	
				Y = 99.4152 - 0.0209 x T	22489F548S	
				Y = 98.7442 - 0.0209 x T	22480D773S	
Tensile Strength Average		5 mg	2	Y = 0.3223 - 0.0011 x T	22489F532S	
				Y = 0.3366 - 0.0011 x T	22489F533S	
				Y = 0.3666 - 0.0011 x T	22489F548S	
				Y = 0.3397 - 0.0011 x T	22480D773S	

KEY: Model 1 – common slope and common intercepts
Model 2 – common slope and separate intercepts
Model 3 – separate slopes and separate intercepts

Figure 1. Data, fitted line, and Confidence Interval for the Stability Batch (22489F533S) of Clarinex™ Reditabs Stored Under 25°C/60%RH Condition



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/s/

Feng Zhou
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Karl Lin
6/7/02 10:42:57 AM
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Concur with review

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STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

NDA Number:	21-312
Applicant:	Schering Corporation
Name of Drug:	Clarinex™ Reditabs
Document Reviewed:	Stability data reports – Dated July 19, 2001
Statistical Reviewer:	Feng Zhou, HFD-715
Chemistry Reviewer:	Craig M. Bertha, Ph.D., HFD-570

I. Introduction

The sponsor submitted the stability data of four batches of Clarinex™ Reditabs 5 mg (NDA 21-312), packaged in aluminum foil blisters, to support its proposed 24-month shelf lives under 25°C/60%RH storage condition.

II. Sponsor's Stability Analysis

The sponsor submitted the stability data reports and the electronic stability data (in SAS transport files) on July 19, 2001. The SAS transport files contain the stability data up to 18 months for two test parameters (Assay and Moisture).

The stability data of four batches were listed in Table A.

Table B contains the specification limits for the parameters the sponsor used to establish the stability for Clarinex™ Reditabs. The sponsor submitted the details of its estimation analysis for two parameters (Assay and Moisture) and proposed an expiration dating period of 24 months for the aluminum foil blisters packaging configuration when the drug products are stored under 25°C/60%RH condition. (p101, vol. 1)

Table A. Summary of all Stability Data Points Submitted by the Sponsor for Clarinex™ Reditabs 5 mg with Blister Packaging Stored Under 25°C/60%RH Condition

		Time Point (month)					
Test	***Batch***	***0***	***3***	***6***	***9***	***12***	***18***
Assay of Desloratadine	22489F532S, 22489F532S, 22489F532S	S	S	S	S	S	S
	22480D773S	S	S	S	S		
Moisture	22489F532S, 22489F532S, 22489F532S	S	S	S	S	S	S
	22480D773S	S	S	S	S		

S = Submitted in electronic copy (July 19, 2001)

Table B. List of Specification limits the Sponsor Used to Establish the Stability For Clarinex™ Reditabs

Test Parameter	Acceptance Criteria
Assay of Desloratadine	[redacted]
Moisture	Not more than [redacted]

The sponsor claimed that the statistical methods used were in accordance with FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs Biologics." The sponsor also claimed that it used the Agency's SAS Stability Analysis Program (STAB) to perform the statistical analysis.

Tables C summarizes the sponsor's statistical results. (p101, vol. 1)

Table C. Summary of Statistical Analyses for the Stability Batches of Clarinex™ Reditabs Stored Under 25°C/60%RH Condition

Test	*Batch*	*Model*	*Estimated Expiration Period*
Assay for Desloratadine	22480D773S	3	[redacted]
	22489F532S		
	22489F533S		
	22489F548S		
Moisture	22480D773S	2	
	22489F532S		
	22489F533S		
	22489F548S		

KEY: Model 1 – common slope and common intercepts
Model 2 – common slope and separate intercepts
Model 3 – separate slopes and separate intercepts

III. Reviewer's Stability Analysis

This reviewer analyzed the data in accordance with FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs Biologics."

Dr. Craig M. Bertha (Chemist reviewer) requested stability analysis of four parameters (Assay, Moisture content, Tensile strength, and Dissolution at the 4 minute sampling interval) using data from three batches (22489F532S, 22489F533S, 22489F548S). The sponsor only submitted the electronic data and detailed statistical analysis for two parameters (Assay and Moisture). Therefore the results of this reviewer's analysis, presented in Table D, are only based on the evaluation of two parameters (Assay and Moisture).

In Table D, the shortest estimated expiration-dating period, [redacted] months, is based on the Assay for the Desloratadine data of three batches. Figure A displays the Assay for Desloratadine data from batch 22489F548S and the fitted line.

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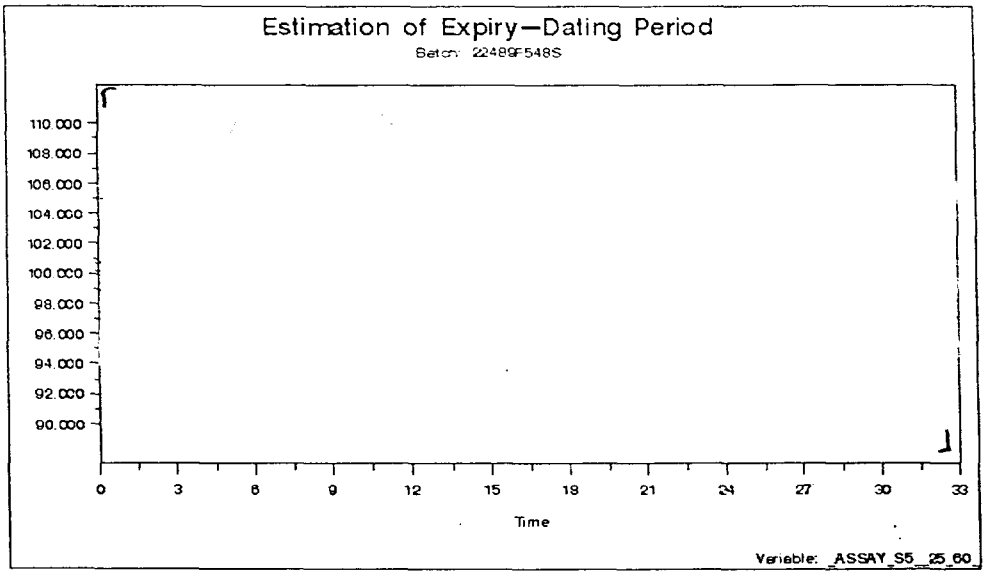
Table D. Summary of Statistical Analyses for the Stability Batches of Clarinex™ Reditabs Stored Under 25°C/60%RH Condition

Test	Specification	Strength	Model	Fitted Line	Batch	Estimated Expiration Date
Assay for	[redacted]	5 mg	3	Y = 99.9114 - 0.0514 x T	22489F532S	[redacted]
Desloratadine	of Label Claim			Y = 98.880 + 0.0067 x T	22489F533S	
				Y = 99.8371 - 0.0838 x T	22489F548S	
Moisture	[redacted]	5 mg	1	Y = 7.1835 + 0.0007 x T	POOLED	

KEY: Model 1 – common slope and common intercepts
Model 2 – common slope and separate intercepts
Model 3 – separate slopes and separate intercepts

Figure A. Data, fitted line. and Confidence Interval for the Stability Batch (22489F548S) of Clarinex™ Reditabs Stored Under 25°C/60%RH Condition



V. Conclusion

The results of this reviewer's analysis based on the evaluation of two parameters (Assay and Moisture) using data from three batches (18-month data) for the aluminum foil blisters packaging configuration, when the drug products are stored under 25°C/60%RH condition, support the 24-month expiration date proposed by the sponsor.

This reviewer's comments may be revised after the additional stability data for the parameters of Tensile strength and Dissolution at the 4 minutes sampling interval are submitted and statistically analyzed.

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/s/

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Karl Lin
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